which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant respectfully traverses the rejection.

The Examiner states that the specification confines its teachings to methods of predicting an increased risk for prostate cancer by comparing the concentration of IGF-I to a reference level, wherein an elevation of at least 100 ng/ml above the reference level indicates a doubling of the risk for prostate cancer. The claims are drawn to methods where even a small increase in IGF-I concentration above a reference level indicates an increased risk for prostate cancer; but it is not clear from the specification what IGF-I elevations are significant, and how elevations less than 100 ng/ml correlate to any risk for prostate cancer. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant respectfully traverses the Examiner's rejection. The specification teaches that there is a significant association between having an IGF-I level above the reference level and risk of prostate cancer. According to the data presented in Table 2, there is a significant linear trend between the circulating IGF-I levels and relative risk of prostate cancer (see page 9, lines 22-24 and page 11, lines 6-11). IGF-I was significantly associated with prostate cancer risk in a univariate analysis, and the association became stronger with further adjustment of the IGF-I levels for the levels of IGFBP-3 (see page 11, lines 1-5). The linear trend was such that after adjusting for IGFBP-3, a 100 ng/ml increase in IGF-I corresponded to an approximate doubling of relative risk when compared to the reference level (see page 11, lines 6-11 and Table 2). The doubling of

risk for a 100 ng/ml elevation of IGF-I is described as a particular point in the linear trend; however, elevations below 100 ng/ml would also correspond to a significant increased risk for prostate cancer, being part of the same linear trend. In addition, IGF-I remained a significant independent predictor of prostate cancer risk even after accounting for other risk factors such as weight, height, body mass index, androgen receptor CAG repeats, and various circulating hormone levels (see page 12, lines 1-5).

Because the specification demonstrates a significant increase in the risk of prostate cancer for IGF-I levels that are above the reference range, Applicant respectfully submits that one skilled in the art would not be required to engage in undue experimentation to practice the invention as claimed. Accordingly, Applicant respectfully requests that the rejection under 35 USC 112, first paragraph, be withdrawn.

The 35 U.S.C. §102(b) rejections

Claims 21-27 are rejected under 35 USC 102(a) as being anticipated by **Mantzouros** (Mantzouros *et al., British Journal of Cancer* 76(9): 1115-1118, 1997). Applicant respectfully traverses the rejection.

The Examiner states that **Mantzouros** teaches a method of predicting risk of prostate cancer where concentrations of IGF-I are measured in healthy individuals and where IGF-I concentrations are measured in test individuals that have either prostate cancer or BPH, and where a risk of prostate cancer is determined by comparing IGF-I levels to a reference. **Mantzouros** teaches that an increase in IGF-I in 60 ng/ml leads to a 91 percent increase in risk of prostate cancer; therefore, **Mantzouros** teaches methods that are the same as those claimed.

Applicant respectfully traverses the Examiner's rejection. In **Mantzouros**, blood samples were collected from individuals with histologically confirmed cases of prostate cancer or BPH, and from healthy individuals (see Abstract). The levels of IGF-I were compared between the cases and controls and found to be overall elevated in the prostate cancer cases; **Mantzouros** found that an increase of 60 ng/ml corresponded to an odds ratio of 1.91, indicating an increased risk of prostate cancer (see *Id.*). **Mantzouros** therefore determined an increased risk of prostate cancer from comparing samples from individuals already having prostate cancer with samples from healthy individuals (see Abstract and Table 1). In contrast, the present specification describes a study in which all individuals were healthy at the time sample collection; all assays reported are from blood specimens collected an average of seven years prior to clinical diagnosis of prostate cancer (see page 8, lines 16-17). Therefore, the study described in the present specification is prospective, whereas the **Mantzouros** study was retrospective. In addition, unlike the teachings of the present specification, because of its retrospective nature the **Mantzouros** study could not rule out possible effects of the cancer itself, or cancer treatment, on IGF-I levels (see the paragraph spanning pages 14-15).

Applicant respectfully contends that because the methods in the present claims are not the same as those taught in **Mantzouros**, the present claims are not anticipated by **Mantzouros**. Accordingly, Applicant respectfully requests that the rejection under 35 USC 102(a) be withdrawn.

The nonstatutory double patenting rejection

Claims 21-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,410,335. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of US 6,410,335 appear to be a species of the more broadly claimed instant inventions.

In order to overcome this rejection, Applicant submits a terminal disclaimer in compliance with 37 CFR 1.321(c). The conflicting patent is commonly owned with the present application. Accordingly, Applicant respectfully requests that the rejection under the nonstatutory double patenting doctrine be withdrawn.

This is intended to be a complete response to the Office Action mailed October 5, 2004. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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